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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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08/781,296 01/13/97 HARLEY

J	OMRF 161 EXAMINER
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HM12/0317

ART UNIT ZEMAN, M	PAPER NUMBER 22
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1643
DATE MAILED:

03/17/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 12/7/98, 12/29/98 + 1/11/99 + 1/21/99
- ☒ This action is FINAL.

- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-5 + 11-18 is/are pending in the application.
- ☐ Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-5 + 11-18 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 21 & 17
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

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DETAILED ACTION

1. Claims 1-5 and 11-18 are pending in this application. Claims 6-10 and 19-26 have been canceled.
2. Applicant's arguments filed 1/12/99 have been fully considered but they are not completely persuasive. The declaration, submitted under 37 CFR 1.132, by Dr Harley has been fully considered and will be addressed below.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. In view of Applicant's amendments or arguments the following objections or rejections are withdrawn:

The objection to the specification for not referencing all priority applications is withdrawn in view of Applicant's statements at page 4 of the response.

All of the art rejections are withdrawn.

Information Disclosure Statement

5. The information disclosure statement filed 1/21/99 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner has carefully reviewed the submitted 1449, and compared it to the marked

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up copy previously remitted to Applicant, and has reviewed all of the recently submitted citations and publications. Again, the examiner reviewed the parent applications of this application for the purposes of finding the references cited upon the information disclosure statement, however a copy of the each and every listed reference was not found. The references considered have been initialed. If Applicant wishes the other references to be considered, a copy of said references and a PTO-1449 listing said references should be submitted. It is noted that Hardgrave et al, and Kaufman et al. do not list a publication year. The publication year of the references is required.

Claim Rejections - 35 USC § 112

6. Claims 4 and 11-18 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "individual at risk" in claim 11 is a relative term which renders the claim indefinite. The term "at risk" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant argues that one of skill in the art would be apprised of the meaning of the term, yet does not set forth evidence to support that assertion. The risk factors to be assessed in the administration of the composition are not clearly set forth. Is the simple infection with EBV the only risk factor involved?

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The term "symptoms associated with" in claim 11 is a relative term which renders the claim indefinite. The term "symptoms associated with an autoimmune disease" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant asserts that one of skill in the art is fully aware of all of the potential symptoms of autoimmune diseases, yet does not provide any evidence to that effect. Applicant is claiming means of treating innumerable autoimmune diseases which have widely disparate (and in many cases non-overlapping) symptoms, such that it is impossible to determine what symptoms would identify a patient as needing the claimed compositions. Many of the symptoms of autoimmune diseases overlap with diseases not of autoimmune origin, and therefore would not necessarily be a relevant indicator for identification of suitable patients.

Claim 4 is rejected as it does not recite the sequence identification number (i.e. SEQ ID NO:) of the relevant peptides sequences in the claims. Correction of this defect is required to fully comply with the sequence rules.

7. Claims 1-5 and 11-18 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous office action.

Claims 1-5 are drawn to an immunogenic composition which can "alleviate or prevent" symptoms of autoimmune disorders. Claims 11-18 are drawn to methods of "preventing or

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alleviating" symptoms of autoimmune disorders. The vaccine comprises modified EBV or a component thereof. The elected species is a nuclear antigen 1 protein lacking the PPPGRRP epitope. The elected autoimmune disease is systemic lupus erythematosus (SLE). Applicant has submitted the declaration under 37 CFR 1.132 of Dr Harley, however this declaration is not sufficient to overcome the rejection.

The specification and the declaration of Dr Harley set forth the association of antibodies to a particular EBNA-1 epitope are tightly associated with the emergence of SLE and RA. These experiments appear to indicate a useful diagnostic application for the prediction of autoimmune disease development (See also claims 10 and 11 of Applicant's recent US Patent 5,637,454). However, these experiments do not correlate with the alleviation, prevention, or lessening of any symptom of any autoimmune disease. As discussed in the interview of 10/20/98, in order for claims drawn to alleviating or preventing symptoms of an autoimmune disorder or alleviating or preventing the disorder itself to be enabled, evidence must be present which correlates to a reasonable degree with the scope of the claim. No evidence has been set forth which shows the lessening of any symptom of an autoimmune disease by the administration of a composition of the invention. The examiner understands the limits of some types of research, yet is bound by statute for enablement. The lack of a viable animal model was discussed at the interview, however that does not release Applicant from the burden of enabling the invention as required by 35 U.S.C. 112, first paragraph. Applicant had tentatively suggested that an experiment done in rabbits showing the lack of development of particular antibodies after immunization with the claimed

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composition could be submitted as evidence, however such evidence is not of record. The experiments submitted in the declaration of Dr Harley used immunizations of the PPPGRRP peptide itself- and not an EBNA antigen lacking those polypeptides. The data discussed by Dr Harley seems to indicate the induction of tolerance to the peptide when the peptide is used for immunization under particular conditions or dosing schedules. The tolerance was measured by the lack of subsequent production of relevant autoantibody. These experiments would support claims drawn to compositions comprising the PPPGRRP polypeptide for inducing tolerance, but not for the methods and compositions as they are now claimed. Applicant has not provided any evidence that an EBNA-1 protein lacking the peptide sequence has any effect on tolerance or autoimmune response.

As set forth previously, the specification appears to be directed to the detection of EBV infection, and correlation of that detection with autoimmune diseases. The specification does not set forth the successful treatment, alleviation, or prevention of any autoimmune disease, or symptom thereof. The term "alleviation" refers to the lessening or cessation of the autoimmune disorder, or symptoms of that disorder. The term "prevention" means that the subject receiving the composition never develops the autoimmune disease or symptoms of that disease, even upon challenge with live unattenuated EBV.

The specification does not set forth any examples wherein the administration of the elected composition in an accepted animal model is able to successfully "alleviate" an already existing autoimmune disease. The specification does not set forth any examples wherein the

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administration of the elected composition totally or partially "prevents" the development of an autoimmune disorder in an accepted animal model. There are no experiments which challenge vaccinated animals with live unattenuated EBV such that the prevention of the autoimmune disease is shown.

The specification does not set forth any direct correlation between the administration of the elected composition, and the development/alleviation/prevention of the elected autoimmune disorder. While antibodies to a particular epitope could be common in a patient with SLE, there is no indication that the administration of the entire protein, lacking that sequence would have any effect upon the clinical course of the disease, whether it be preventing the development of that disease, or the treatment of that disease. It is also not clear that the administration of the claimed composition would prevent the development of antibodies to the deleted region when challenged with native virus. If the epitope is such a strong SLE epitope, it is possible that despite the vaccine, the patient may develop antibodies to the PPPGRRP motif upon challenge with native virus. SLE patients have many "abnormal" antibodies present in their serum. (Abnormal in the sense that normal patients do not have antibodies to the same epitopes) It is presently not known whether the presence of the antibodies is the cause or the effect of the autoimmune disease; i.e. do the antibodies cause the symptoms of SLE, or does the course of SLE allow the development of abnormal antibodies.

The specification and evidence provided in the declaration could support claims drawn to a diagnostic application for the diagnosis of an autoimmune disease. The specification and

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evidence provided in the declaration may support claims drawn to the induction of tolerance to autoimmunity associated antigens by the administration of the particular peptides, using a particular dosage schedule.

Conclusion

8. No claim is allowed.

9. The following references, cited, but not relied upon, are considered pertinent to

Applicant's disclosure:

US Patent 5,637,454 Harley

US Patent 5,679,774 Wolf

US Patent 5,723,283 Classen

US Patent 5,874,531 Strominger et al.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

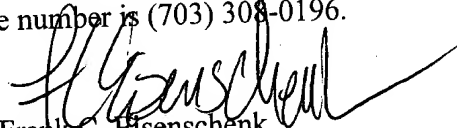
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can normally be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Eisenschenk, can be reached on (703) 308-0452.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
March 15, 1999


Frank C. Eisenschenk
Primary Examiner, Group 1600